Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2101544

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Supplementary Methods

Changes in Conduct and Protocol Amendments

There were 3 amendments to the protocol before the primary analysis. The first amendment to the protocol was adopted before any study-related procedures began.

In the first amendment (15 September 2020), the time to begin counting COVID-19 cases after vaccination was decreased from ≥28 days post-vaccination to ≥14 days post-vaccination (primary endpoint). Other changes included the following: implementation of the selected dose level of 5×10^{10} vp for Ad26.COV2.S based on data from the first-in-human study VAC31518COV1001; additional changes based on emerging epidemiology information and advancing insights, including the determination of the sample size, further details of the case definitions for COVID-19, and the addition of target percentages (min/max) for enrollment of certain age groups; changes made in response to feedback received from Health Authorities, partners, and the community; and some minor editorial changes.

The second amendment (29 October 2020) included the following changes: clarification that all participants who have a reverse transcriptase polymerase chain reaction (RT-PCR) positive finding for SARS-CoV-2, even if asymptomatic, will be followed until there are 2 consecutive negative RT-PCR tests; correction of errors, including the clarification that blood will be drawn on Day 29 for biomarker RNAseq analyses (PAXgene tube), which is needed to assess the current objectives; and minor editorial changes.

The third amendment (14 December 2020) included the following changes: the occurrence of molecularly confirmed, moderate to severe–critical COVID-19, with onset at least 28 days post-vaccination was added as a co-primary endpoint in addition to the current primary endpoint counting as of 14 days post-vaccination. The applicable secondary and exploratory endpoints were updated similarly to also include COVID-19 cases with onset at least 28 days post-vaccination. In addition, the total sample size was reduced from 60,000 to approximately 40,000 participants. The protocol was further amended to change the conditions for monitoring whether efficacy greater than 30% is achieved using the sequential monitoring algorithm: (1) the need for a follow-up of 8 weeks for 50% of the participants prior to an initial look at an efficacy signal if the other conditions are met was removed, (2) the minimum number of COVID-19 cases meeting the primary case definition needed to start the efficacy monitoring was modified to at least 42 instead of 20 to increase the robustness of the package in case of an early efficacy signal. Furthermore, additional secondary and exploratory objectives and endpoints were added; the Clinical Evaluation Committee was replaced by the Clinical Severity Adjudication Committee; the definitive role of the Clinical Severity Adjudication Committee in defining the severity of cases of COVID-19 was clarified; the utilization of tokenization and matching procedures was added; clarification of procedures for unblinding of study participants who may become eligible to receive an authorized/licensed COVID-19 vaccine during the course of the study was included; and additional clarifications and minor editorial changes were added.

The introduction of co-primary endpoints at ≥14 and ≥28 days post-vaccination in amendment 3 was done because it was recognized from preclinical and human immunology results that

protection and human immune responses might occur as early as Day 14. It was also recognized that, as immune response matured, higher levels of protection might be achieved. Therefore, to capture these two concepts, the co-primary endpoints were introduced. The sample size was reduced because the incidence of COVID-19 was substantially higher than assumed at the time of protocol planning. Based on the observed incidence and modeling, there was a high degree of probability that an efficacy signal meeting the pre-specified criteria in the amendment would be reached at or before the time at which 50% of participants would have been followed for 8 weeks post-vaccination.

Study Pause

A committee consisting of the representatives of the sponsor and collaboration partners, along with the principal investigator (the protocol safety review team [PSRT]) and the Janssen Medical Safety Council monitored safety in a blinded manner, including the study vaccination pausing rules (applicable to Stages 1a and 2a only). If a study vaccination was considered to raise significant safety concerns (and a specific set of pausing criteria had been met), further vaccination of participants was paused. On 11 October 2020, the sponsor was informed of a serious adverse event (SAE) in Study COV3001 that met a study pausing rule. As a precautionary measure, vaccinations in all studies in the program were paused. After DSMB review, resumption of study vaccinations from 27 October 2020 was recommended.

Inclusion and Exclusion Criteria

Every potential participant must have satisfied all of the following criteria to be enrolled in the study: participants must provide consent indicating that he or she understands the purpose, procedures and potential risks and benefits of the study, and is willing to participate in the study; participants must be willing and able to adhere to the prohibitions and restrictions specified in the protocol; for Stages 1a and 1b, participant must be ≥18 to <60 years of age on the day of signing the informed consent form (ICF); for Stages 2a and 2b, participants must be ≥60 years of age on the day of signing the ICF; for Stages 1a and 2a, in the investigator's clinical judgement, the participant must be either in good or stable health, including a BMI <30 kg/m^2.

Participants may have underlying illnesses (not associated with increased risk of progression to severe COVID-19), as long as their symptoms and signs are stable and well-controlled. If participants are on medication for a condition not part of the comorbidities listed in the full protocol available online, the medication dose cannot have been increased within 12 weeks preceding vaccination and is expected to remain stable for the duration of the study. Participants would be included on the basis of relevant medical history and BMI measurement at screening.

For stages 1b and 2b, in the investigator's clinical judgement, participants may have had a stable and well-controlled medical condition including comorbidities associated with an increased risk of progression to severe COVID-19 (eg, stable/well controlled HIV infection). If participants were on medication for a medical condition (including comorbidities associated with an increased risk of progression to severe COVID-19), the medication dose cannot have been increased within 12 weeks preceding vaccination and must be expected to remain stable for the duration of the study. Participants would be included on the basis of relevant medical history and BMI measurement at screening.

Participants with HIV infection must have had documented stable/well-controlled infection, defined as documented CD4 cell count ≥300 cells/μL within 6 months prior to screening, or documented HIV viral load <50 copies/mL within 6 months prior to screening. Participants with HIV must have been on a stable anti-retroviral treatment (ART) for 6 months (unless the change was due to tolerability, in which case the regimen could be for only the previous 3 months; changes in formulation were allowed; nationwide guidelines that require transition from one ART regimen to another were allowed) and the participant must have been willing to continue his/her ART throughout the study as directed by his/her local physician.

Before randomization, participants must be either not of childbearing potential, or of childbearing potential and practicing an acceptable effective method of contraception and agree to remain on such a method of contraception from providing consent until 3 months after administration of study vaccine. Use of hormonal contraception should have started at least 28 days before the administration of study vaccine. All participants of childbearing potential must have had a negative highly sensitive urine pregnancy test at screening and a negative pregnancy test on the day of and prior to study vaccine administration.

Participants must have agreed to not donate bone marrow, blood, and blood products from the study vaccine administration until 3 months after receiving the study vaccine.

Any potential participant who meets any of the following criteria would be excluded from participating in the study: participant has a clinically significant acute illness (not including minor illnesses such as diarrhea or mild upper respiratory tract infection) or temperature ≥38.0ºC (100.4°F) within 24 hours prior to the planned study vaccination (randomization at a later date was permitted at the discretion of the investigator and after consultation with the sponsor); has a known or suspected allergy or history of anaphylaxis or other serious adverse reactions to vaccines or their excipients (including specifically the excipients of the study vaccine); has abnormal function of the immune system resulting from clinical conditions (eg, autoimmune disease or potential immune mediated disease or known or suspected immunodeficiency, or participant on hemodialysis) expected to have an impact on the immune response of the study vaccine.

Participants with clinical conditions stable under non-immunomodulator treatment (eg, autoimmune thyroiditis, autoimmune inflammatory rheumatic disease such as rheumatoid arthritis) could be enrolled at the discretion of the investigator. Non-immunomodulator treatment was allowed as well as steroids at a non-immunosuppressive dose or route of administration.

Participants were excluded if they had chronic or recurrent use of systemic corticosteroids within 6 months before administration of study vaccine and during the study. A substantially immunosuppressive steroid dose was considered to be ≥2 weeks of daily receipt of 20 mg of prednisone or equivalent. Ocular, topical, or inhaled steroids were allowed.

Participants were excluded if they received antineoplastic and immunomodulating agents or radiotherapy within 6 months before administration of study vaccine and during the study; received treatment with Ig in the 3 months or exogenous blood products (autologous blood

transfusions are not exclusionary) in the 4 months before the planned administration of the study vaccine or had any plans to receive such treatment during the study; received or planned to receive licensed live attenuated vaccines within 28 days before or after planned administration of study vaccine; received or planned to receive other licensed (not live) vaccines within 14 days before or after planned administration of study vaccine; previously received a coronavirus vaccine; received an investigational drug (including investigational drugs for prophylaxis of COVID-19) within 30 days or used an invasive investigational medical device within 30 days or received investigational immunoglobulin or monoclonal antibodies within 3 months, or received convalescent serum for COVID-19 treatment within 4 months or received an investigational vaccine (including investigational Adenoviral-vectored vaccines) within 6 months before the planned administration of the study vaccine or were currently enrolled or planned to participate in another investigational study during the course of this study. Participation in an observational clinical study was allowed at the investigator's discretion.

Efforts were made to ensure inclusion of participants who have not been previously enrolled in coronavirus studies and to prevent participants from subsequently enrolling in other coronavirus studies during their participation in this study. The use of any coronavirus vaccine (licensed or investigational) other than Ad26.COV2.S was disallowed at any time prior to vaccination and during the study, except under the conditions described in the full protocol available online.

Participants were excluded if they were pregnant or planning to become pregnant within 3 months after study vaccine administration; had a history of an underlying clinically significant acute or chronic medical condition or physical examination findings for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well- being) or that could prevent, limit, or confound the protocol-specified assessments; had a contraindication to intramuscular injections and blood draws (eg, bleeding disorders); has had major psychiatric illness which in the investigator's opinion would compromise the participant's safety or compliance with the study procedures; could not communicate reliably with the investigator; were, in the opinion of the investigator, unlikely to adhere to the requirements of the study, or unlikely to complete the full course of vaccination and observation.

Exclusion criteria for Stages 1a and 2a included comorbidities that were or might be associated with an increased risk of progression to severe COVID-19, ie, moderate to severe asthma; chronic lung diseases such as chronic obstructive pulmonary disease (COPD) (including emphysema and chronic bronchitis), idiopathic pulmonary fibrosis and cystic fibrosis; diabetes (including type 1 or type 2); serious heart conditions, including heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, and pulmonary hypertension; moderate to severe high blood pressure; obesity (BMI $\geq$30 kg/m^2); chronic liver disease, including cirrhosis; sickle cell disease; thalassemia; cerebrovascular disease; neurologic conditions (dementia); end stage renal disease; organ transplantation; cancer; HIV infection and other immunodeficiencies; hepatitis B infection; and sleep apnea; history of or current Parkinson's disease; seizures; ischemic strokes; intracranial hemorrhage; encephalopathy and meningoencephalitis; history of malignancy within 1 year before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or other malignancies with minimal risk of recurrence); history of acute polyneuropathy (eg, Guillain-Barré syndrome); surgery requiring hospitalization (defined as inpatient stay for longer than 24 hours or overnight stay), within 12

weeks before vaccination, or will not have fully recovered from surgery requiring hospitalization, or had surgery requiring hospitalization planned during the time the participant was expected to participate in the study or within 6 months after study vaccine administration; or had chronic active hepatitis B or hepatitis C infection per medical history.

Study Procedures for Reporting Symptoms of COVID-19 and Collection of Swabs

Participants were given a Symptoms of Infection with Coronavirus-19 (SIC) questionnaire (a measure of symptom severity developed per best practice),[1] a pulse oximeter, and a swab self-collection kit. They were asked to report any COVID-19 symptoms immediately through an electronic clinical outcome assessment tool, and received a twice-weekly prompt. Those with symptoms completed the SIC daily and took pulse oximeter readings three times daily from the day symptoms began for the duration of illness. Based on the SIC, investigators contacted participants on the day or day after symptoms began to assess whether the symptoms qualified as suspected COVID-19. Participants took nasal swabs at home on the day or day after symptoms began and every other day until there were two consecutive negative swabs; in addition, study staff took nasal swabs at least once. Swabs were refrigerated in sterile saline and stored in a freezer before shipment to the central laboratory on dry ice.

Safety Definitions

Serious adverse events included those that resulted in death, were life-threatening, required hospitalization (or prolonging of existing hospitalization), resulted in persistent or significant disability, were congenital anomalies, were a suspected transmission of any infectious agent via a medicinal product, or were considered medically important based on investigator judgment. Medically-attended adverse events (MAAEs) included adverse events requiring hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason. New onset of chronic diseases were collected as part of the MAAEs. Routine study visits were not considered medically attended visits.

In the subset of participants recording solicited local and systemic adverse events, solicited local adverse events included injection site pain/tenderness, erythema, and swelling at the injection site. The largest diameter of any erythema and swelling was measured and recorded daily. Solicited systemic events included fatigue, headache, myalgia, nausea, and temperature monitoring for fever.

COVID-19 Case Definitions

Molecular confirmation of SARS-CoV-2 infection by a central laboratory (University of Washington Virology laboratory) was used for case definition analysis. A SARS-CoV-2 positive RT-PCR (Abbot) test result from any available respiratory tract sample (eg, nasal swab sample, sputum sample, throat swab sample, saliva sample) or other sample was required for each case definition.

Moderate COVID-19 cases were defined by 1) a positive RT-PCR test for SARS-CoV-2 and 2) two or more of the following symptoms (new or worsening): fever or chills, cough, heart rate ≥90 beats/minute, muscle or body pain, headache, new loss of taste or smell, sore throat, red or

bruised-looking feet or toes, nausea, vomiting, or diarrhea; or one or more of the following signs or symptoms: shortness of breath, respiratory rate >20 breaths/minute, clinical or radiologic evidence of pneumonia, deep vein thrombosis, or abnormal oxygen saturation (but above 93%).

Severe–critical COVID-19 cases were defined by a positive RT-PCR test for SARS-CoV-2 with one of the following features: respiratory failure; evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors); respiratory rate >30 breaths/minute; heart rate ≥125 beats/minute; oxygen saturation of 93% or less (ambient air at sea level), or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen <300 mm Hg; intensive care unit admission; significant acute renal, hepatic, or neurologic dysfunction, or death.

Mild Covid-19 cases were defined by a positive RT-PCR test for SARS-CoV-2 and at any time during observation, one of the following symptoms, but does not meet the definition for moderate or severe–critical COVID-19: fever (≥38.0°C or ≥100.4°F), sore throat, malaise (loss of appetite, generally unwell, fatigue, physical weakness), headache, muscle pain (myalgia), gastrointestinal symptoms, cough, chest congestion, runny nose, wheezing, skin rash, eye irritation or discharge, chills, new or changing olfactory or taste disorders, red or bruised looking feet or toes, or shaking chills or rigors.

Laboratory Methods

Sequencing Methods

Next-generation sequencing was performed using the Swift Biosciences SNAP Version 2.0, performed at the Virology Laboratory of the University of Washington, Department of Laboratory Medicine and Pathology (UW Virology). The SNAP assay utilizes multiple overlapping amplicons in a single tube to prepare ready-to-sequence libraries. Primer pairs used in SNAP are designed for generating libraries from first- or second-strand cDNA produced from viral isolates or clinical specimens. This unique design enables successful SARS-CoV-2 library preparation from samples with low viral titers and provides powerful solutions for the confident detection of nucleotide variants. The Swift Biosciences SARS-CoV2 Version 2.0 kit (Catalog # CovGl V2-96) has been optimized to achieve additional genome coverage. The assay is optimized for Illumina sequencing platforms. A full clinical validation with determination of analytical sensitivity and specificity, limit of detection, accuracy, and assay precision (reproducibility and repeatability) has been performed.

Only S gene information was considered, and whole viral genome sequences have not yet been analyzed. However, the assignment of approximate lineages based on the predefined set of S amino acid substitutions agreed with the known circulating lineages in the considered countries based on the GISAID database (GISAlD 2021). To classify SARS-CoV-2 S sequences into their most probable lineages the following predefined substitution profiles were used:

I. Variant 20I/501Y.Vl (lineage B1.1.7) = del 69 + del 70 + del 144 + N501Y + A570D + D614G + P681H + T761I + S982A + D1118H

II. Variant 20H/50lY.V2 (lineage B.l.351) = K417N + E484K + N501Y + D614G + A701V

III. Variant 20J/501Y.V3 (lineage P.l) = Ll8F + T20N + P26S + Dl38Y + Rl90S + K417T + E484K + N501Y + D614G + H655Y + Tl027I

IV. Variant CAL.20C (lineage B.l.429) = S13I + Wl52C + L452R + D614G

V. Ref + E484K (lineage P.2) = All strains containing substitution E484K, but neither 20H/501Y.V2 nor 20J/501Y.V3

VI. Reference Sequence = D614G, and all other remaining substitutions, but excluding variants falling into profiles I-V

Samples taken as close as possible to the start of symptoms from individuals with SARS-CoV-2 viral load >200 copies/mL were selected. Priority for sequencing was given to samples from participants in the United States, South Africa and Brazil with symptom onset ≥14 or ≥28 days post-vaccination, and with at least moderate or severe–critical illness. As many samples as possible will be sequenced as part of the ongoing study.

An initial analysis evaluating viral load among symptomatic cases did not indicate any differences between placebo recipients and vaccine recipients with breakthrough infection. Further analysis of an association between viral load and number and intensity of symptoms will be reported at a later date.

Statistical Analysis Methods

Population analysis sets
The full analysis set (FAS) included all randomized participants with a documented study vaccine administration, regardless of the occurrence of protocol deviations and serostatus at enrollment. Analyses of safety was performed on the FAS. Vaccine efficacy analyses were repeated using the FAS.

The safety subset was a subset of the FAS for analysis of solicited and unsolicited AEs.

The per-protocol efficacy population (PP) included participants in the FAS who received study vaccine, were seronegative at the time of vaccination, and who had no other major protocol deviations that were judged to possibly impact the efficacy of the vaccine. If serostatus was missing, the subject was assumed to be seronegative. If the subject had a PCR positive result at baseline, then the subject was excluded from the per-protocol set. The primary analysis of vaccine efficacy was based on the PP population. The PP was the main analysis population for efficacy analyses. The PP population was selected as the main population for efficacy analysis to provide an assessment of vaccine efficacy in individuals without current or previous SARS-CoV-2 infection and who had no protocol deviations likely to impact vaccine efficacy. The reasons for exclusion are shown in Supplementary Figure S2. It should be noted that our population did include participants with comorbidities known to be associated with development of severe COVID-19 illness.

The reasons for excluding participants from the per-protocol analysis were mainly baseline seropositivity (9.6%). Additional reasons included RT-PCR positivity at baseline (0.5%) and major protocol deviations that would possibly impact efficacy (0.2%). Exclusions were balanced between randomized groups (Figure S2). Therefore, the evaluation of the co-primary endpoints in baseline seronegative participants is not expected to be impacted by the choice of the per-protocol set over the full analysis set. Compared with the per-protocol set, one additional moderate to severe–critical case with onset ≥14 days post-vaccination was identified in the full analysis set and no additional cases with onset ≥28 days post-vaccination. Given the large sample size and high number of cases, this would not alter the conclusions.

Sample size calculation

The study target number of events (TNE) was determined using the following assumptions: (1) VE for molecularly confirmed, moderate to severe–critical SARS-CoV-2 infection of 60%; (2) approximately 90% power to reject a null hypothesis of H0: VE ≤30%; (3) type 1 error rate α=2.5% to evaluate VE of the vaccine regimen (employing the sequential probability ratio test to perform a fully sequential design analysis); (4) randomization ratio of 1:1 for active versus placebo.

Under these assumptions, the total TNE to compare the active vaccine versus placebo equals 154.

For SAEs, based on a total sample size of approximately 40,000 participants, the observation of 0 events was associated with a 2-sided 95% upper limit for the true event rate being <0.015%.

Hypothesis testing

For hypothesis testing of primary and secondary objectives, the family-wise error rate was controlled at 2.5%. Adjustment for interim testing was done via truncated sequential probability ratio test for the co-primary endpoints. The evaluation of secondary endpoints was adjusted for multiple testing of multiple endpoints (Table S3) using a graphical approach according to the method of Bretz et al 2009[2] and potential stopping at an interim analysis evaluation through a Pocock boundary using Wang-Tsiatis with Delta=0.5. The timepoint and order of evaluation of multiple endpoints was done according to the graphical method detailed in the Statistical Analysis Plan.

A successful primary efficacy conclusion will require:

1. Establishing the hypothesis H_1: VE>30% for each co-primary endpoint with a VE point estimate ≥50%). The study is designed to test the co-primary hypotheses of vaccine efficacy (VE) in the PP population. For both co-primary endpoints the following hypothesis will be tested: H_0: VE ≤30% versus H_1: VE >30% and each hypothesis will be evaluated at a 2.5% one-sided significance level.

   AND

2. A favorable split vaccine:placebo for the subset of primary endpoints meeting the severe–critical COVID-19 case definition (expressed as a VE point estimate against severe–critical

COVID-19 molecularly confirmed endpoints ≥50%) and a minimum of 5 events in the placebo group. This requirement needs to be met separately for severe–critical events with start at least 14 days after vaccination and for severe–critical events with start at least 28 days after vaccination.

Both conditions 1. and 2. will simultaneously have to be met for both co-primary endpoints at the same calendar timepoint.

Timing of evaluation of co-primary objective
The interim monitoring for the primary analysis could start as soon as the following conditions are met:

1. A minimum of 6 COVID-19 primary endpoint cases for the ≥60 years age group with onset at least 28 days after vaccination
2. At least 42 cases meeting the primary endpoint definition of moderate to severe–critical COVID-19 with onset at least 28 days after vaccination
3. A subset of at least 5 cases meeting the definition of severe–critical COVID-19 with onset at least 28 days after vaccination

No interim evaluation will be done, until those conditions are fulfilled

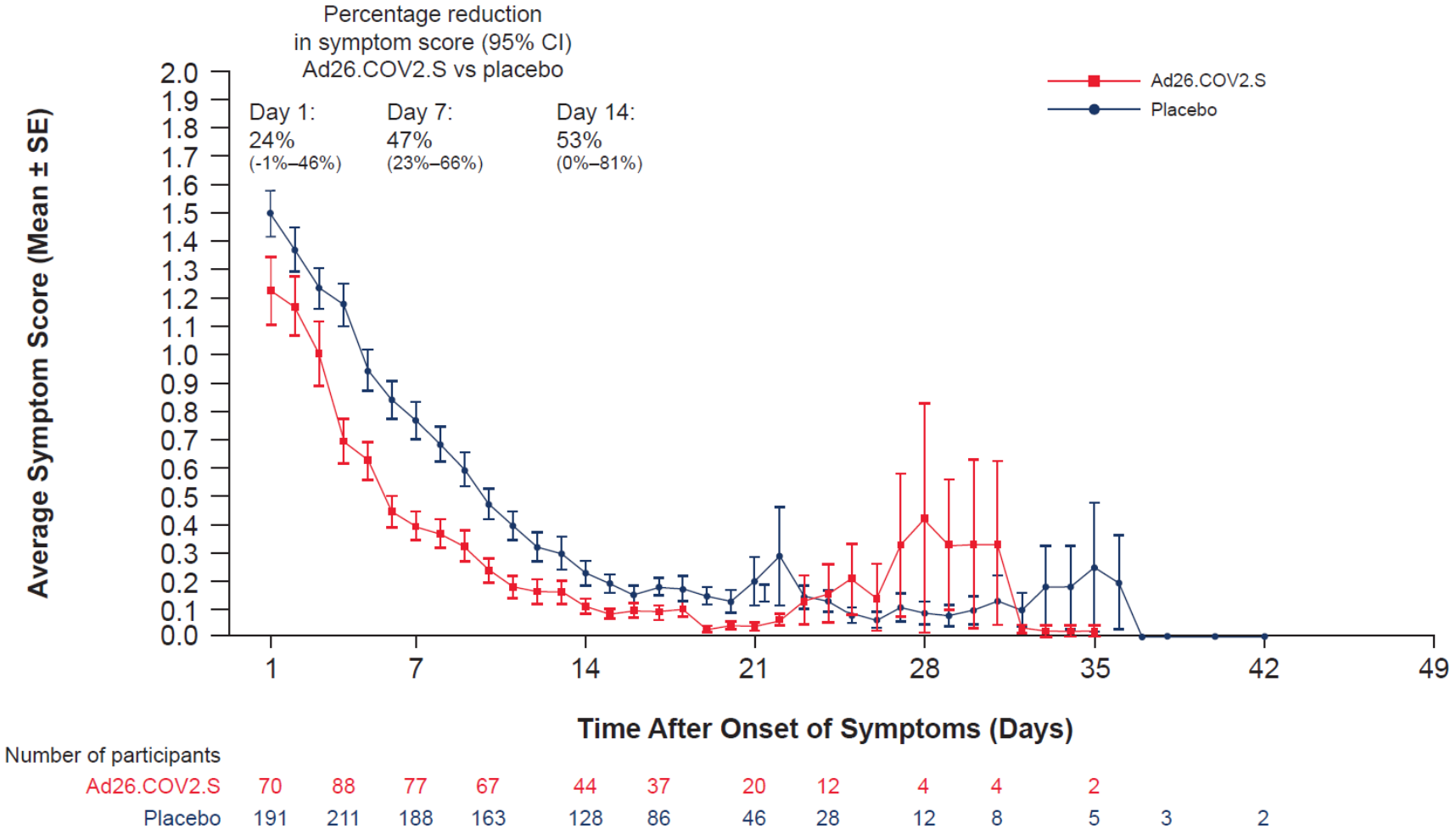
Missing values
Follow-up time was calculated as the time since vaccination until the event or the last available timepoint in the database (either when the subject discontinued from the study, when the subject was unblinded, or if the subject was ongoing: the cut off date for analysis). Missing values for baseline serology were assumed negative. Missing values for covariates were not imputed. The results were tabulated separately for the subgroup with missing covariate data.

For the Symptoms of Infection with Coronavirus-19 (SIC) questionnaire, total scores were calculated based on the severity ratings for all symptoms completed by the participant per day and in cases where more than 75% of the items needed to calculate the score was not collected, then the value for that score was set to missing.

Supportive analysis
A supportive analysis using a Cox proportional hazards regression model of time to moderate to severe–critical COVID-19 events was also used to estimate VE. The analysis was stratified for age (≥60 years, <60 years) and comorbidities (with or without comorbidities). The strata were based on the values in the database (which may differ to the strata as recorded in the Interactive Web Response System). Stratification for (mobile) site unit at the time of randomization was done to ensure balance in exposure to SARS-CoV-2 between randomized groups over time because of the spatiotemporal evolution of the epidemic. However, including all stratification factors (age by comorbidity by [mobile] site) in the analysis would result in a large number of 'empty strata' (i.e. without cases), as the TNE of 154 is substantially lower than the anticipated

number of stratification levels. Therefore, no summaries were provided by this stratification factor (mobile unit).

Figure S1. Total Score with the SIC Questionnaire for Cases of Moderate Severity With Onset At Least 28 Days After Vaccination (Per-Protocol Set, Seronegative At Baseline, RT-PCR-positive Cases from All Sources)



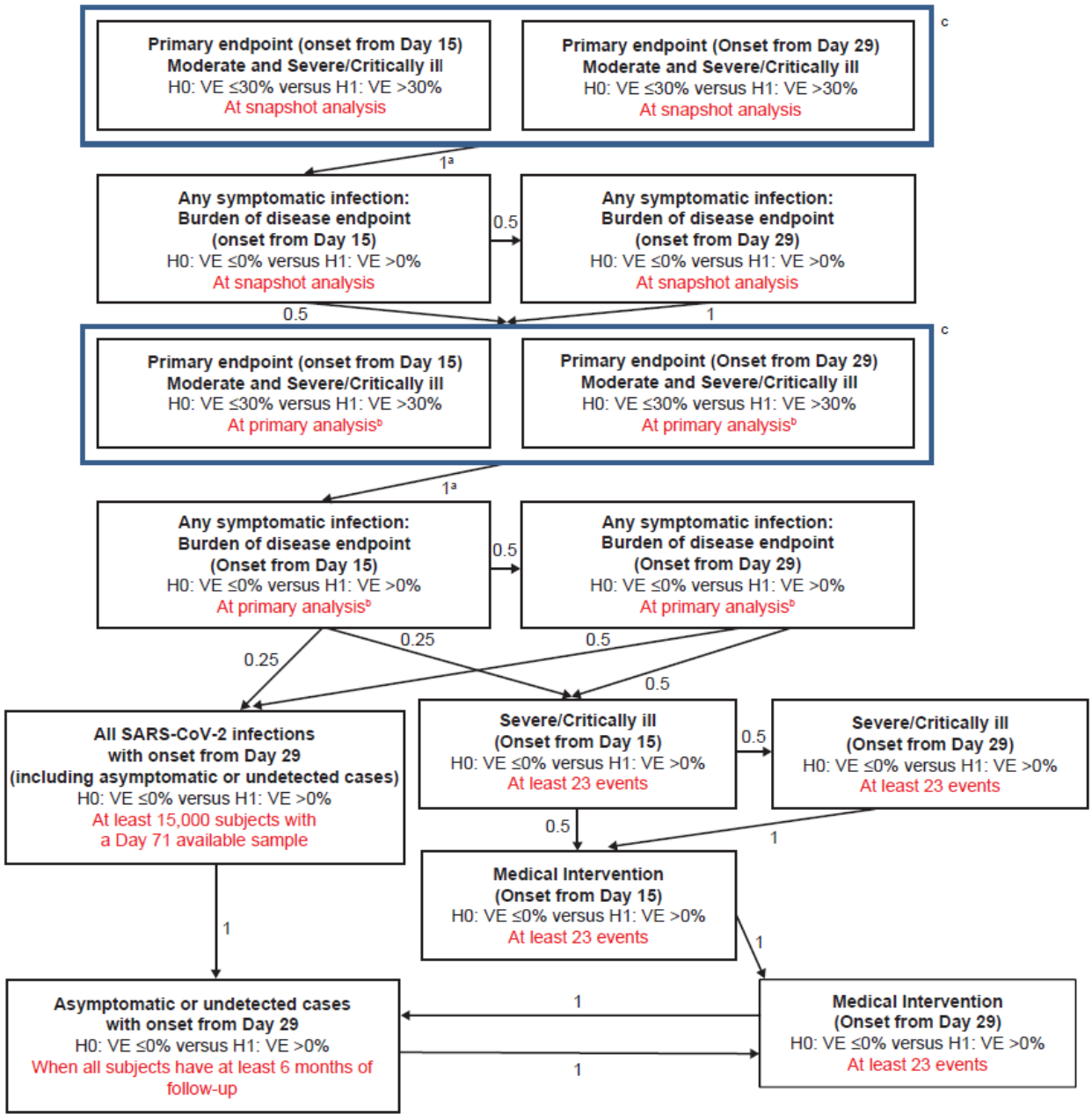
Participants completed an electronic SIC questionnaire recording COVID-19 symptoms daily from the day symptoms began for the duration of illness. The questionnaire included 30 questions, of which 25 had a severity rating scale of 0−10 (0=none, 10=worst possible). The total score shown in the graph is the mean

of all scores for each day during the COVID-19 episode. The percentage values shown at Days 1, 7 and 14 refer to the percentage reduction in symptom score for Ad26.COV2.S vaccine relative to placebo.

Symptom severity was an exploratory endpoint. The reduction in symptoms versus placebo and associated CIs on Days 1, 7 and 14 were calculated post-hoc using an unpooled, Satterthwaite-based two-sided 95% CI to support interpretation of the pre-specified descriptive summary over time.

CI: confidence interval; SIC: Symptoms of Infection with Coronavirus-19; SE: standard error

Figure S2. Graphical Approach for the Hypothesis Evaluation



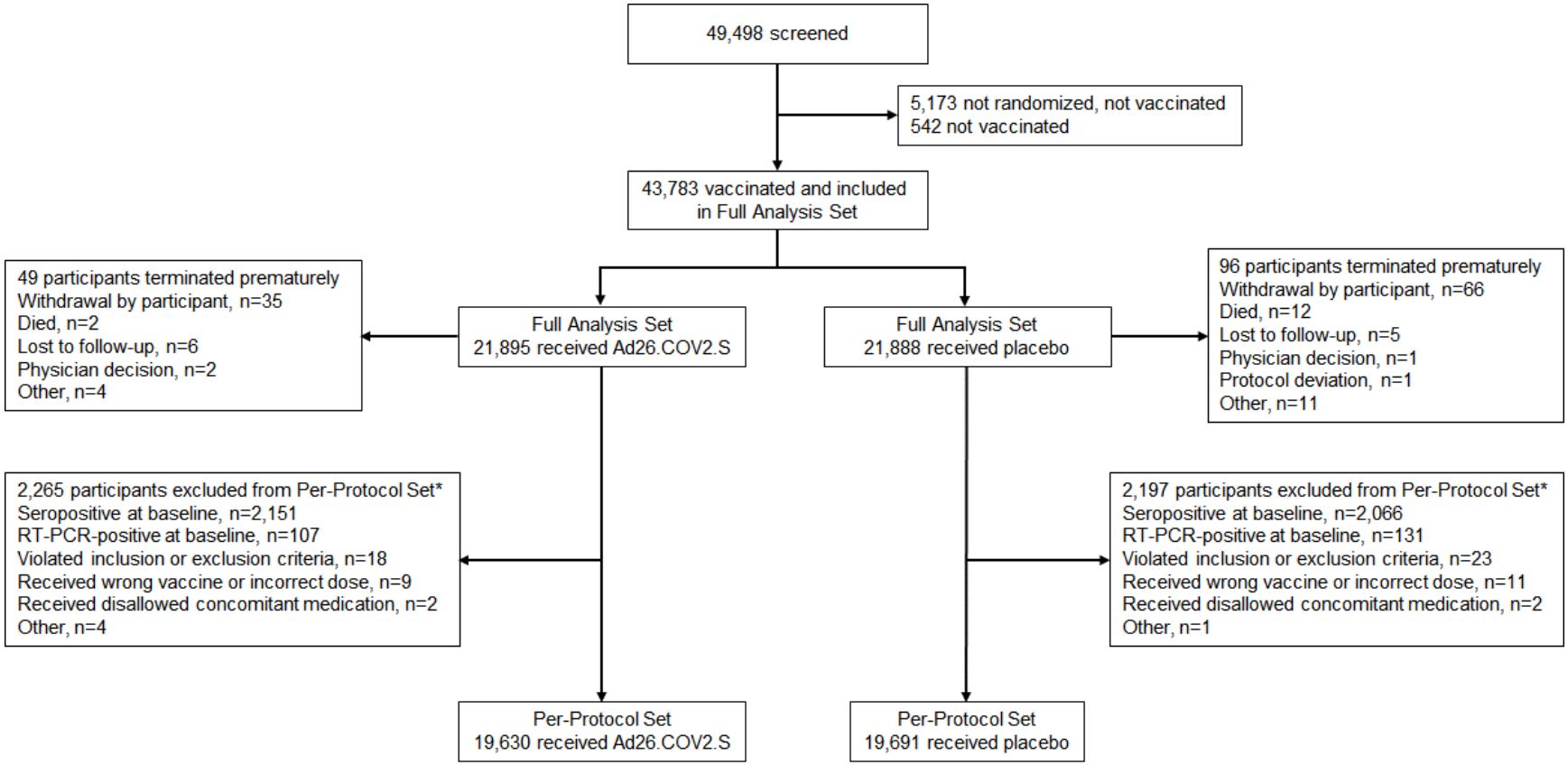
[a]The alpha level passed down to the secondary tests was based on a group sequential design with a single interim analysis and with information fraction determined by the primary endpoint including all events with onset at least 28 days post-vaccination (i.e., number of primary events with onset at least 28 days post vaccination at the time of data base cut off [when the respective efficacy boundary is crossed by each co-primary endpoint and the data requirement are met] divided by the TNE) and corresponding alpha-level obtained from a Pocock boundary.

[b]If an efficacy signal was triggered before the required 8-week follow-up after vaccination of 50% of participants was reached, an additional analysis would be performed when that follow-up timepoint was reached (8-week median follow-up timepoint), to support health authority interactions. The analysis at the time of the 8-week median follow-up would be considered the primary analysis. Note that the primary analysis was triggered upon a positive recommendation from the DSMB, after the FDA-specified median 8-week follow-up was reached, and prespecified data requirements were met, and hence the snapshot as indicated in Figure S1 was not performed.

[c]When testing the co-primary endpoints at the time of the snapshot analysis or at the time of the primary analysis, both would have to reach significance in order to continue with the hierarchical testing.

DSMB: Data and Safety Monitoring Board; FDA: Food and Drug Administration; TNE: target number of events; VE: vaccine efficacy

Figure S3. Participant Disposition



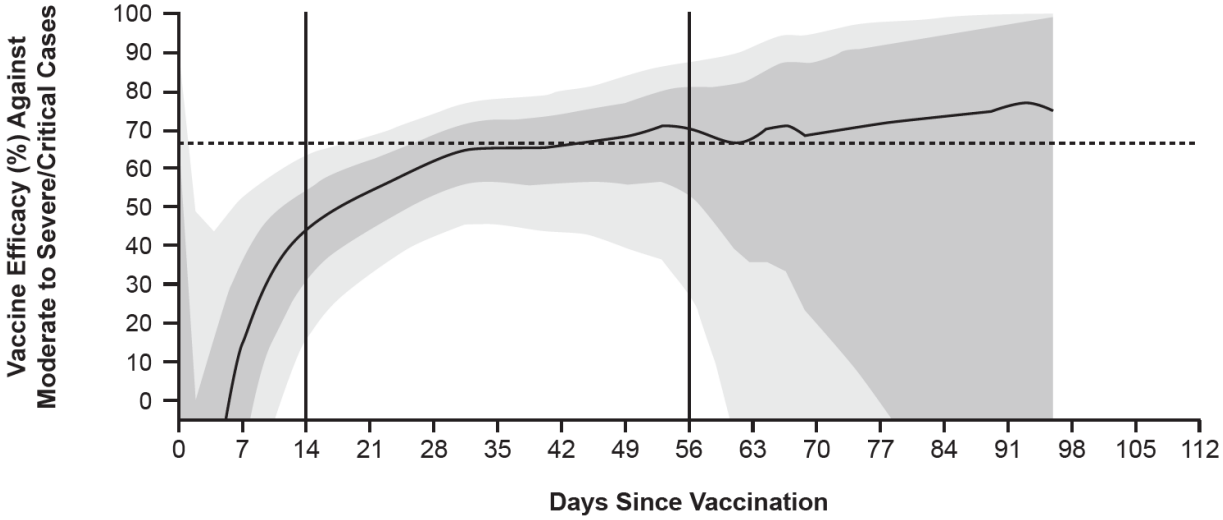
*Participants could be excluded for more than one reason

Data cut-off for the analysis was January 22, 2021. The full analysis set included all randomized participants who received study vaccine. The per-protocol set comprised participants who received study vaccine, were seronegative and RT-PCR-negative at the time of vaccination and had no protocol deviations likely to impact vaccine efficacy.

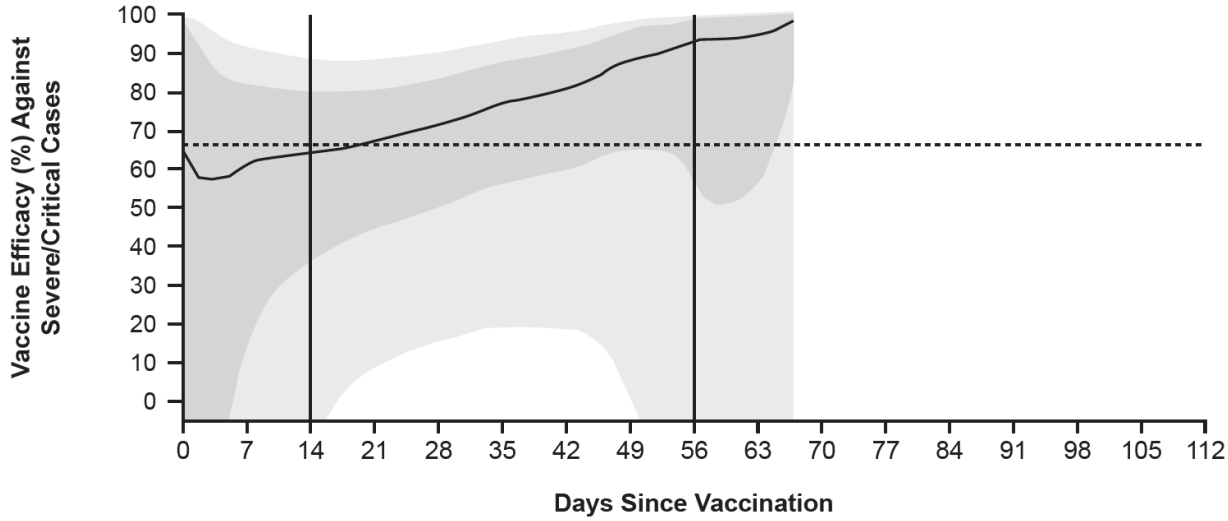
RT-PCR: reverse transcriptase polymerase chain reaction

Figure S4. Vaccine Efficacy Over Time

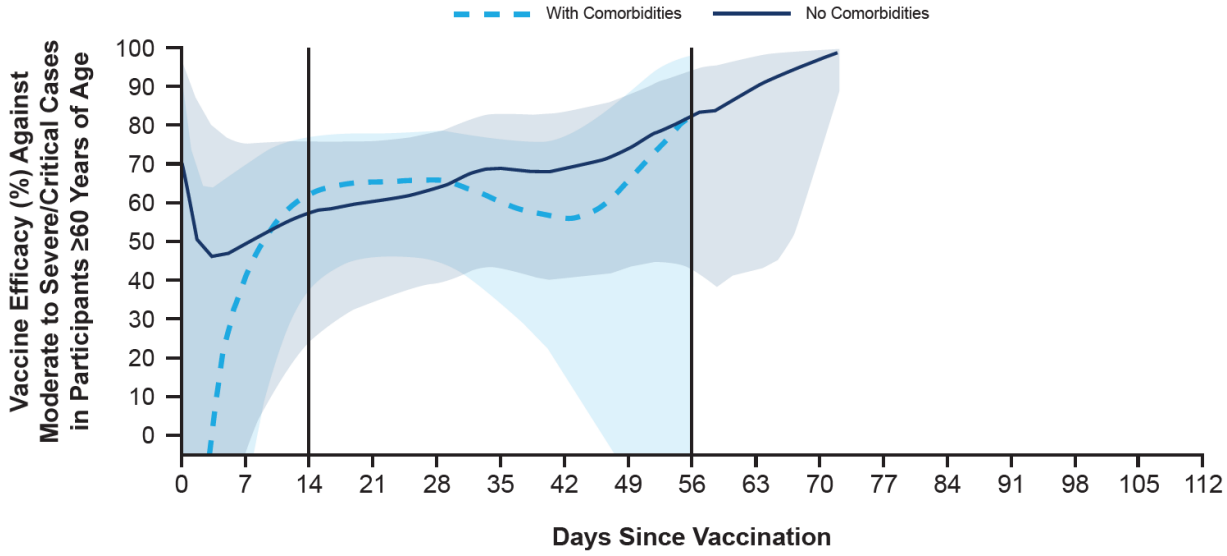
A. Vaccine efficacy against moderate to severe–critical cases over time (FAS, seronegative at baseline, centrally-confirmed cases)



B. Vaccine efficacy against severe–critical cases over time (FAS, seronegative at baseline, centrally-confirmed cases)



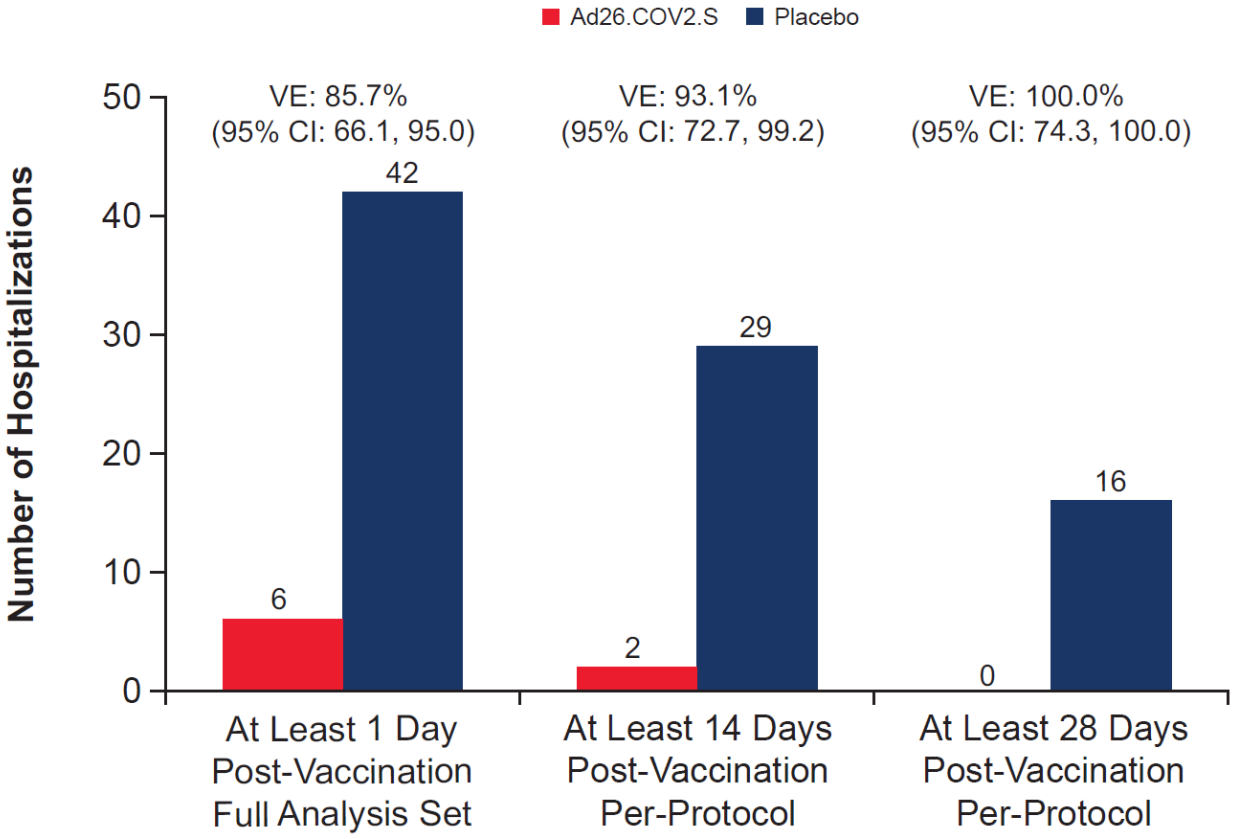
C. Vaccine efficacy against moderate to severe–critical cases in participants ≥60 years of age with and without comorbidities over time (seronegative at baseline, RT-PCR-positive cases from all sources)



The hazard was smoothed over a period 21 days, and the analysis was based on the methods of Gilbert et al.[3] In panels A and B, the dark grey shading shows the 95% pointwise CI and the light grey shading shows the 95% simultaneous CI. In panel C, the blue shading shows the 95% pointwise CI for the dataset with comorbidities and the grey shading shows the 95% pointwise CI for the dataset with no comorbidities. The vaccine efficacy estimates become difficult to interpret with small numbers. Therefore, the vaccine efficacy estimate over time before 14 days may be unreliable. Furthermore, since the number of participants with follow-up substantially decreases beyond 56 days, the uncertainty as reflected in the width of the CIs around the estimated vaccine efficacy curve increased beyond that time point.

CI: confidence interval; FAS: full analysis set; RT-PCR: reverse transcriptase polymerase chain reaction

Figure S5. Vaccine Efficacy Against COVID-19 Related Hospitalizations (Seronegative At Baseline, RT-PCR-positive Cases from All Sources)



Case onset was the earliest of either the onset of the AE associated with COVID-19 or the onset of the COVID-19 episode as determined in the pre-specified algorithm (based on signs and symptoms from the eCOA and MA-COV forms, as well as RT-PCR testing).

The pre-specified analysis of hospitalization included data from MRU questionnaires only. Because not all MRU forms were available at the time of the primary analysis, a post-hoc analysis was done to analyze all hospitalizations linked to COVID-19 based on MRU, SAE and MA-COV forms (post-hoc analysis shown here).

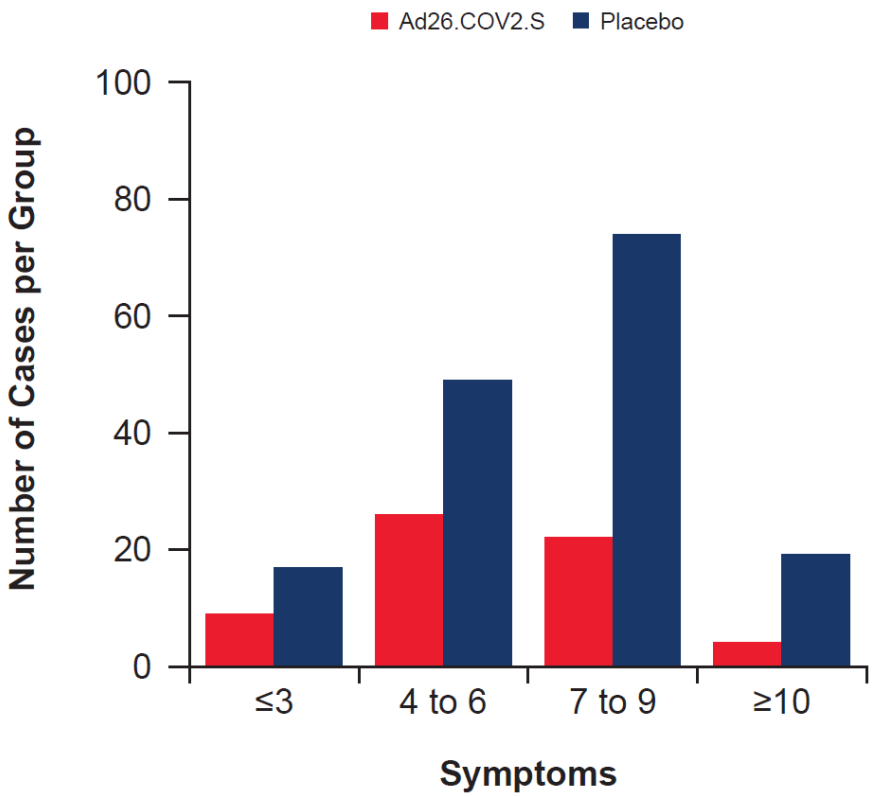
FAS baseline seronegative: at-risk population N=19,744 vaccine, N=19,822 placebo; PY 3202.8 vaccine, 3211.6 placebo.

PP with onset ≥14 days: at-risk population N=19,514 vaccine, N=19,544 placebo, excludes participants who were RT-PCR positive between Day 1 and Day 14; PY 3125.8 vaccine, 3125.1 placebo.

PP with onset ≥28 days: at-risk population N=19,306 vaccine, N=19,178 placebo, excludes participants who were RT-PCR positive between Day 1 and Day 28; PY 3106.3 vaccine, 3083.9 placebo.

CI: confidence interval; eCOA: electronic clinical outcome assessment; FAS: full analysis set; MA-COV: medically-attended COVID-19; MRU: medical resource utilization; PP: per-protocol; PY: person years; RT-PCR: reverse transcriptase polymerase chain reaction; SAE: serious adverse event; VE: vaccine efficacy

Figure S6. Number of Symptoms in Participants With Moderate COVID-19 With Onset At Least 28 Days After Vaccination (Per-Protocol Set, Seronegative At Baseline, Centrally-Confirmed)



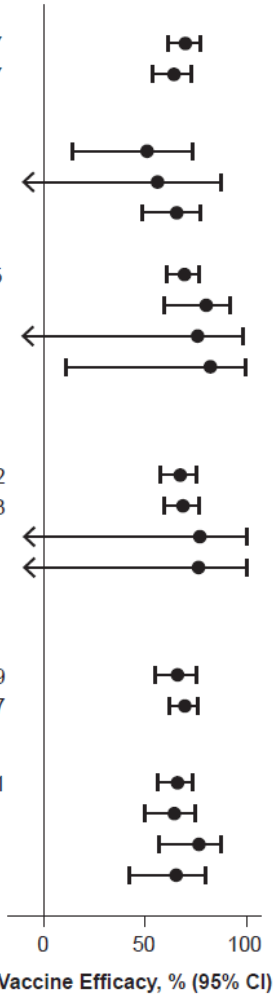
Post-hoc analysis. The y-axis represents the number of cases and the height of the bars represents the number of cases observed in each category.

CI: confidence interval

Figure S7. Vaccine Efficacy Against Moderate to Severe–Critical COVID-19 By Subgroups for Cases with Onset ≥14 days post-vaccination (A) and Onset ≥28 days post-vaccination (B) (Per-Protocol Set, Seronegative At Baseline, RT-PCR-positive Cases from All Sources)

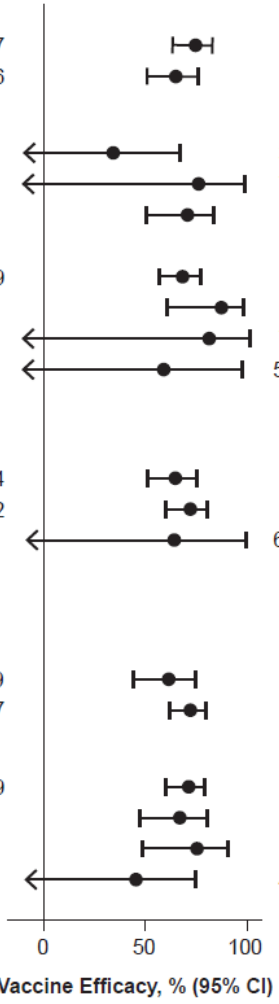
A.

Subgroup	Ad26.COV2.S (N=19,514)[1] no. events/no. participants	Ad26.COV2.S (N=19,514)[1] PY	Placebo (N=19,544)[1] no. events/no. participants	Placebo (N=19,544)[1] PY	Vaccine Efficacy, % (95% CI)[2]
Sex					
Male	85 / 10,861	1,739.00	269 / 10,832	1715.87	68.8% (60.1-75.9)
Female	88 / 8,649	1,374.18	240 / 8,708	1372.57	63.4% (53.1-71.7)
Race					
Amer. Indian/Alaskan	21 / 1,634	279.00	41 / 1,621	275.41	49.4% (12.4-71.6)
Asian	6 / 714	99.46	12 / 649	90.61	54.4% (-31.1-86.0)
Black or African Amer.	37 / 3,362	495.73	101 / 3,361	491.43	63.7% (46.6-75.8)
Native Hawaiian/other	1 / 54	8.03	0 / 44	6.63	
White	94 / 12,123	1,975.43	288 / 12,133	1958.25	67.6% (59.0-74.6)
Multiple	10 / 1,028	166.58	48 / 1,080	170.75	78.6% (57.3-90.4)
Unknown	2 / 261	39.60	8 / 269	41.35	73.9% (-30.8-97.3)
Not Reported	2 / 337	49.94	11 / 385	54.36	80.2% (9.3-97.9)
Missing	0 / 1	0.12	0 / 2	0.25	
Ethnicity					
Hispanic/Latino	81 / 8,733	1,418.62	237 / 8,869	1,429.32	65.6% (55.5-73.6)
Not Hispanic/Latino	88 / 10,289	1,620.33	257 / 10,184	1,587.73	66.4% (57.1-74.0)
Not Reported	2 / 318	48.62	8 / 330	48.34	75.1% (-24.5-97.4)
Unknown	2 / 173	26.09	7 / 160	23.52	74.2% (-35.3-97.4)
Missing	0 / 1	0.21	0 / 1	0.16	
Comorbidities					
Yes	70 / 7,777	1,138.79	194 / 7,798	1,130.89	64.2% (52.7-73.1)
No	103 / 11,737	1,975.09	315 / 11,746	1,958.17	67.6% (59.4-74.3)
Age and Comorbitities[3]					
18-59, no	89 / 8,346	1,433.46	258 / 8,411	1,428.21	65.6% (56.1-73.3)
18-59, yes	48 / 4,404	671.45	131 / 4,371	660.99	63.9% (49.4-74.7)
≥60, no	14 / 3,391	541.63	57 / 3,335	529.95	76.0% (56.3-87.6)
≥60, yes	22 / 3,373	467.35	63 / 3,427	469.91	64.9% (42.2-79.4)



B.

Subgroup	Ad26.COV2.S (N=19,306)[4] no. events / no. participants	PY	Placebo (N=19,178)[4] no. events / no. participants	PY	Vaccine Efficacy, % (95% CI)[2]
Sex					
Male	54 / 10,764	1,732.44	176 / 10,649	1,704.17	69.8% (58.9-78.2)
Female	59 / 8,538	1,367.13	148 / 8,525	1,361.06	60.3% (46.0-71.2)
Race					
Amer. Indian/Alaskan	18 / 1,628	278.35	26 / 1,604	274.41	31.7% (-29.4-64.8)
Asian	2 / 689	97.93	7 / 626	89.07	74.0% (-36.5-97.4)
Black or African Amer.	21 / 3,330	493.65	66 / 3,300	487.28	68.6% (48.0-81.8)
Native Hawaiian/other	1 / 54	8.03	0 / 43	6.56	
White	64 / 11,994	1,966.98	187 / 11,912	1,944.39	66.2% (54.8-74.9)
Multiple	4 / 1,018	165.99	28 / 1,055	169.23	85.4% (58.4-96.3)
Unknown	1 / 259	39.48	5 / 262	40.93	79.3% (-85.3-99.6)
Not Reported	2 / 333	49.72	5 / 374	53.74	56.8% (-164.1-95.9)
Missing	0 / 1	0.12	0 / 2	0.25	
Ethnicity					
Hispanic/Latino	59 / 8,688	1,415.66	153 / 8,741	1,421.44	61.3% (47.4-71.8)
Not Hispanic/Latino	52 / 10,131	1,610.06	163 / 9,957	1,573.12	68.8% (57.2-77.6)
Not Reported	2 / 317	48.56	5 / 323	47.85	60.6% (-140.8-96.3)
Unknown	0 / 169	25.77	3 / 156	23.28	
Missing	0 / 1	0.21	0 / 1	0.16	
Comorbidities					
Yes	44 / 7,684	1,132.99	105 / 7,626	1,119.99	58.6% (40.6-71.6)
No	69 / 11,622	1,967.27	219 / 11,552	1,945.87	68.8% (59.0-76.6)
Age and Comorbitities[3]					
18-59, no	58 / 8,267	1,428.23	180 / 8,254	1,418.29	68.0% (56.8-76.6)
18-59, yes	29 / 4,350	668.12	79 / 4,273	654.75	64.0% (44.3-77.3)
≥60, no	11 / 3,355	539.04	39 / 3,298	527.58	72.4% (45.0-87.3)
≥60, yes	15 / 3,334	464.88	26 / 3,353	465.24	42.3% (-13.1-71.6)



[1]At-risk population: excludes participants who were RT-PCR positive between Day 1 and Day 14

[2]Unadjusted CI

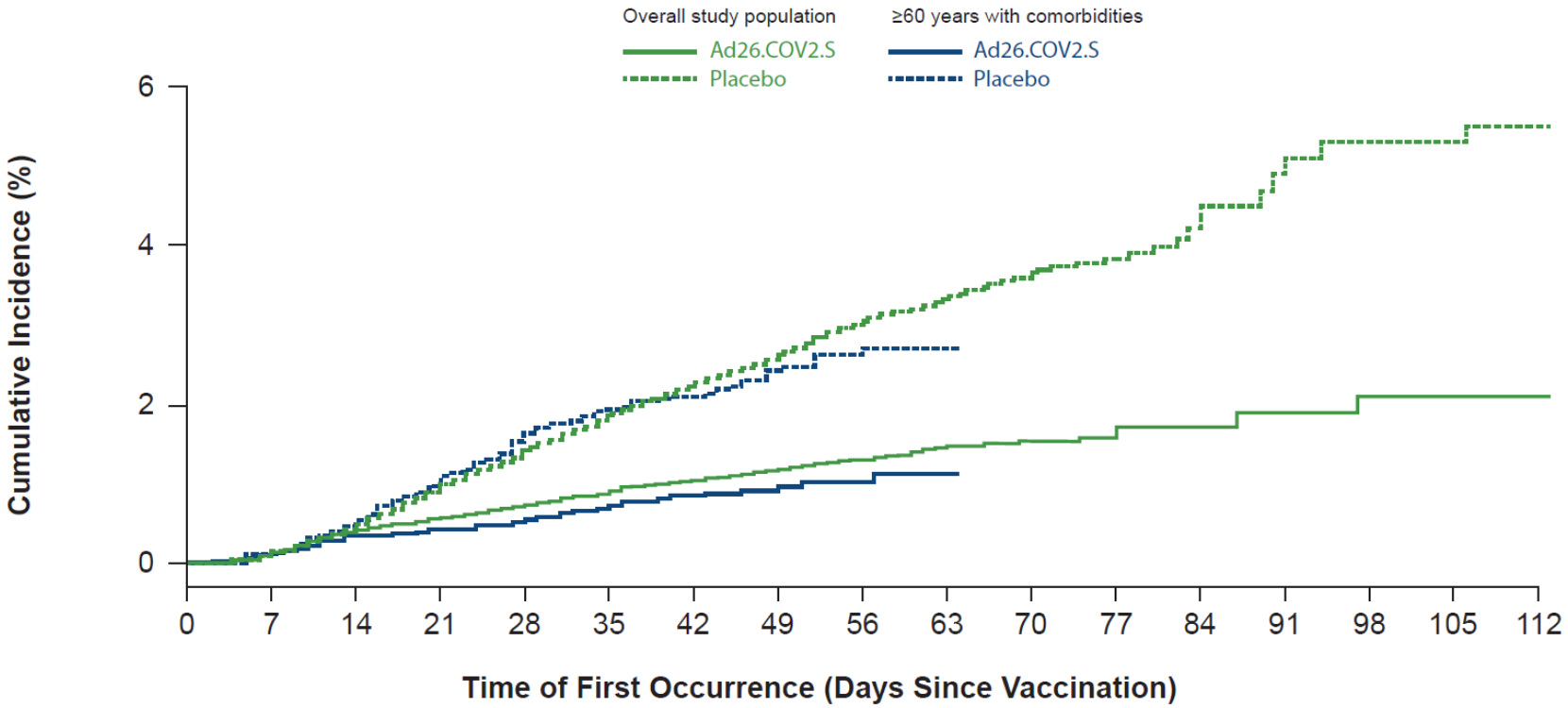
[3]The p-value for the 3-way interaction, VE by age and comorbidity, in a Cox proportional hazards model on moderate to severe–critical cases was not significant (p=0.46 [Day>14] and p=0.25 [Day >28]). While lack of significant interaction does not prove absence of interaction, the analyses show lack of evidence to support that there is a difference in VE among the subgroups

[4]At-risk population: excludes participants who were RT-PCR positive between Day 1 and Day 28

The American Indian/Alaskan Native category included American Indian/Alaskan Native participants residing in the United States (n=92 Ad26.COV2.S, n=95 placebo) and Indigenous people from South America (n=1,991 Ad26.COV2.S, n=1,965 placebo).

CI: confidence interval; PY: person-years; RT-PCR: reverse transcriptase polymerase chain reaction; VE: vaccine efficacy

Figure S8. Cumulative Incidence of Moderate to Severe–Critical COVID-19 With Onset At Least 1 Day After Vaccination in Participants ≥60 Years with Comorbidities Versus the Overall Population (Full Analysis Set, Seronegative At Baseline, RT-PCR-Positive Cases from All Sources)



Participants at Risk

Ad26.COV2.S	19,739	19,717	19,656	19,619	19,586	19,545	18,504	14,872	10,896	7,798	3,984	1,466	712	484	483	482	142
Placebo	19,809	19,789	19,717	19,612	19,521	19,405	18,324	14,741	10,745	7,677	3,843	1,432	707	483	478	476	132
Ad26.COV2.S	3,413	3,409	3,400	3,395	3,391	3,381	3,213	1,883	1,013	376	25						
Placebo	3,474	3,470	3,457	3,440	3,417	3,400	3,213	1,859	978	376	12						

Cumulative incidence curves/N at risk truncated 7 days after last event

CI: confidence interval; RT-PCR: reverse transcriptase polymerase chain reaction

Table S1. Objectives and Endpoints of the Trial

Objectives	Endpoints
Co-Primary	
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a], moderate to severe–critical COVID-19[b], as compared to placebo, in SARS-CoV-2 seronegative adults	• First occurrence of molecularly confirmed[a], moderate to severe–critical COVID-19[b], with onset at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed[a], moderate to severe–critical COVID-19[b], with onset at least 28 days post-vaccination (Day 29)
Secondary[e]	
Efficacy	
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a], severe–critical COVID-19[b], as compared to placebo	• First occurrence of molecularly confirmed[a], severe–critical COVID-19[b], with onset at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed[a], severe–critical COVID-19[b], with onset at least 28 days post-vaccination (Day 29)
To demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a], moderate to severe–critical COVID-19[b], as compared to placebo, in adults regardless of their serostatus	• First occurrence of molecularly confirmed[a], moderate to severe–critical COVID-19[b], with onset 1 day post-vaccination • First occurrence of molecularly confirmed[a], moderate to severe–critical COVID-19[b], with onset at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed[a], moderate to severe–critical COVID-19[b], with onset at least 28 days post-vaccination (Day 29)
To evaluate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed[a] moderate to severe–critical COVID-19[b] as compared to placebo, with onset 1 day after study vaccination	First occurrence of molecularly confirmed[a], moderate to severe–critical COVID-19[b] with onset 1 day after study vaccination
To assess the effect of Ad26.COV2.S on COVID-19 requiring medical intervention (based on objective criteria) compared to placebo	• First occurrence of COVID-19 requiring medical intervention (such as a composite endpoint of hospitalization, intensive care unit [ICU] admission, mechanical ventilation, and extracorporeal membrane oxygenation [ECMO], linked to objective measures such as decreased oxygenation, X-ray or computed tomographic [CT] findings) and linked to any molecularly confirmed[a], COVID-19[b,c] at least 14 days post-vaccination (Day 15) • First occurrence of COVID-19 requiring medical intervention and linked to any

	molecularly confirmed[a], COVID-19[b,c] at least 28 days post- vaccination (Day 29)
To assess the effect of Ad26.COV2.S on SARS-CoV-2 viral ribonucleic acid (RNA) load compared to placebo for moderate to severe–critical COVID-19[b]	Assessment of the SARS-CoV-2 viral load by quantitative reverse-transcriptase polymerase chain reaction (RT-PCR), in participants with molecularly confirmed[a], moderate to severe–critical COVID-19[b] by serial viral load measurements during the course of a COVID-19 episode
To assess the effect of Ad26.COV2.S on molecularly confirmed[a] mild COVID-19[c]	• First occurrence of molecularly confirmed[a], mild COVID-19b, at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed[a], mild COVID-19b, at least 28 days post-vaccination (Day 29)
To assess the effect of Ad26.COV2.S on COVID-19 as defined by the United States (US) Food and Drug Administration (FDA) harmonized case definition[d]	• First occurrence of molecularly confirmed[a] COVID- 19[b] at least 14 days post-vaccination (Day 15) • First occurrence of molecularly confirmed[a] COVID- 19[b] at least 28 days post-vaccination (Day 29)
To assess the effect of Ad26.COV2.S on all molecularly confirmed[a] symptomatic COVID-19[b,c,] as compared to placebo	• Burden of disease (BOD) endpoint[f] derived from the first occurrence of molecularly confirmed[a] symptomatic COVID-19[b,c] (meeting the mild, moderate or severe–critical COVID-19 case definition) with onset at least 14 days post- vaccination (Day 15). • BOD endpoint[f] derived from the first occurrence of molecularly confirmed[a] symptomatic COVID-19[b,c] (meeting the mild, moderate or severe–critical COVID-19 case definition) with onset at least 28 days post-vaccination (Day 29).
To assess the effect of Ad26.COV2.S on occurrence of confirmed asymptomatic or undetected infections with SARS-CoV-2, as compared to placebo	Serologic conversion between baseline (Day 1; pre- vaccination), Day 71, 6 months, and 1-year post- vaccination using an enzyme-linked immunosorbent assay (ELISA) and/or SARS-CoV-2 immunoglobulin assay that is dependent on the SARS-CoV-2 nucleocapsid (N) protein.
To assess the efficacy of Ad26.COV2.S in the prevention of SARS-CoV-2 infection (both symptomatic and asymptomatic infections combined, that are serologically and/or molecularly confirmed[a]), as compared to placebo	First occurrence of SARS-CoV-2 infection (serologically and/or molecularly confirmed[a]) with onset at least 28 days after vaccination (Day 29)

Safety	
To evaluate safety in terms of serious adverse events (SAEs; during the entire study), medically-attended adverse events (MAAEs; until 6 months post- vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants	Occurrence and relationship of SAEs (during the entire study), MAAEs (until 6 months post-vaccination), and MAAEs leading to study discontinuation (during the entire study) for all participants following vaccination
In a subset of participants, to evaluate the safety and reactogenicity in terms of solicited local and systemic adverse events (AEs) during 7 days after vaccination, and in terms of unsolicited AEs during 28 days post- vaccination	Occurrence, intensity, duration, and relationship of solicited local and systemic AEs during 7 days following vaccination and of unsolicited AEs during 28 days post-vaccination
Immunogenicity	
In a subset of participants, to evaluate the immunogenicity of Ad26.COV2.S, as compared to placebo	Analysis of antibodies binding to the SARS-CoV-2 S protein by ELISA
Exploratory (selected)	
To evaluate patient-reported outcomes (PROs) in relation to the presence of SARS-CoV-2 infection and the presence, severity and duration of COVID-19 signs and symptoms in participants who received Ad26.COV2.S as compared with placebo	Presence, severity and duration of COVID-19 signs and symptoms Confirmation of SARS-CoV-2 infection by molecular testing
To assess the difference in severity of cases in participants who received Ad25.COV2.S as compared to placebo	Reduction in severity of COVID-19 signs and symptoms

[a]Molecularly confirmed COVID-19 is defined as a positive SARS-CoV-2 viral RNA result using a RT-PCR assay (Abbott) at the University of Washington.

[b]Per case definition for moderate to severe–critical COVID-19 (see Section 8.1.3.1 in the protocol).

[c]Per case definition for mild COVID-19 (see Section 8.1.3.2 in the protocol).

[d]Per case definition for COVID-19 according to the US FDA harmonized case definition (see Section 8.1.3.3 in the protocol).

[e]All secondary endpoint analyses will occur in the per-protocol (PP) analysis set, in seronegative participants unless otherwise indicated.

[f]For more information and the definition of the BOD endpoint, refer to Section 9.5.2 Secondary Endpoints in the protocol.

Table S2. Definition of Endpoints Utilizing a Post-Hoc Analysis

Endpoint Label	Endpoint definition
COVID-19 requiring Medical Intervention	First occurrence of COVID-19 requiring medical intervention defined as requiring (prespecified endpoint): Hospitalization, ICU admission, mechanical ventilation, ECMO, linked to objective measures such as decreased oxygenation, X-ray or CT findings, and linked to any molecularly confirmed[a], COVID-19[b,c] during a COVID-19 episode with onset at least 14 days and at least 28 days post vaccination (see Table S1) This information was collected based on MRU questionnaire. Because not all MRU questionnaires were available at the time of the primary analysis for COVID-19, an additional analysis was done based on available information from the SAE. Based on the request of the US FDA, an analysis was added post hoc to analyze all hospitalizations linked to COVID-19 based on MRU, SAE or MA-COV forms.

[a]Molecularly confirmed COVID-19 is defined as a positive SARS-CoV-2 viral RNA result using a RT-PCR assay (Abbott) at the University of Washington.

[b]Per case definition for moderate to severe–critical COVID-19 (see Section 8.1.3.1 in the protocol).

[c]Per case definition for mild COVID-19 (see Section 8.1.3.2 in the protocol).

Table S3. Listing of Alpha Levels Used and Split at the Analysis Timepoints: Per-Protocol Set

Endpoint	Timing of analysis	Total number of cases	Number of cases in vaccine group	Alpha level[1]	Information fraction
Primary endpoint with onset at least 14 days after vaccination[2]	Primary Analysis	464	116	0.05**	-
Primary endpoint with onset at least 28 days after vaccination[2]	Primary Analysis	259	66	0.05**	1.68
All symptomatic infections (BOD) with onset at least 14 days after vaccination	Primary Analysis	468	117	0.05**	-
All symptomatic infections (BOD) with onset at least 28 days after vaccination	Primary Analysis	261	66	0.025**	-
All severe cases with onset at least 14 days after vaccination	Primary Analysis	74	14	0.025**	-
All severe cases with onset at least 28 days after vaccination	Primary Analysis	39	5	0.0125**	-
All cases requiring medical intervention with onset at least 14 days after vaccination	Primary Analysis	10	2	0.05	-
All cases requiring medical intervention with onset at least 28 days after vaccination	Primary Analysis	5	0	0.05	-
All other endpoints	Primary Analysis			0.05	

[1]Used for the calculation of the (adjusted) (1-Alpha)x100% confidence intervals.
[2]Same alpha used for non-confirmed cases.
The adjusted CI implements type I error control for multiple testing and is presented upon meeting the prespecified testing conditions (** indicates adjusted).

Table S4. Comorbidity Characteristics at Baseline of Study Participants (Full Analysis Set)

Comorbidity	**Ad26.COV2.S (N=21,895)**	**Placebo (N=21,888)**	**All (N=43,783)**
No comorbidity – no. (%)	12,959 (59.2)	12,966 (59.2)	25,925 (59.2)
One or more comorbidity – no. (%)	8,936 (40.8)	8,922 (40.8)	17,858 (40.8)
Asthma	262 (1.2)	300 (1.4)	562 (1.3)
Cancer	112 (0.5)	114 (0.5)	226 (0.5)
Cerebrovascular disease	78 (0.4)	80 (0.4)	158 (0.4)
Cystic fibrosis	1 (<0.1)	3 (<0.1)	4 (<0.1)
Chronic kidney disease	112 (0.5)	118 (0.5)	230 (0.5)
COPD	231 (1.1)	206 (0.9)	437 (1.0)
Serious heart condition	497 (2.3)	511 (2.3)	1,008 (2.3)
Hypertension	2,225 (10.2)	2,296 (10.5)	4,521 (10.3)
ICP from blood transplant[1]	43 (0.2)	36 (0.2)	79 (0.2)
ICP from organ transplant	7 (<0.1)	3 (<0.1)	10 (<0.1)
Liver disease	103 (0.5)	103 (0.5)	206 (0.5)
Hepatitis B[2]	18 (17.5)	6 (5.8)	24 (11.7)
Hepatitis C[2]	6 (5.8)	8 (7.8)	14 (6.8)
Neurologic condition	82 (0.4)	125 (0.6)	207 (0.5)
Obesity	6,277 (28.7)	6,215 (28.4)	12,492 (28.5)
Pulmonary fibrosis	10 (<0.1)	9 (<0.1)	19 (<0.1)
Sickle cell disease	13 (0.1)	5 (<0.1)	18 (<0.1)
Type 1 diabetes mellitus	105 (0.5)	90 (0.4)	195 (0.4)
Type 2 diabetes mellitus	1,600 (7.3)	1,594 (7.3)	3,194 (7.3)
Thalassemia	16 (0.1)	30 (0.1)	46 (0.1)

[1]Immunocompromised state from blood or bone marrow transplant, immune deficiencies, use of corticosteroids, or use of other immunosuppressing medicines

[2]The denominator for the percentage calculation is the number of participants with liver disease

COPD: chronic obstructive pulmonary disease; ICP: immunocompromised state

Table S5. Follow-up Time According to Age and Presence or Absence of Comorbidities (Full Analysis Set)

Follow-up	Ad26.COV2.S	Placebo	All
Overall population, N	21,895	21,888	43,783
Participants with ≥8 weeks follow-up, %	54.6	54.6	54.6
Median follow-up post-vaccination, days	58.0	58.0	58.0
18−59 years overall, n	14,564	14,547	29,111
Participants with ≥8 weeks follow-up, %	62.8	63.1	63.0
Median follow-up post-vaccination, days	61.0	61.0	61.0
18−59 years, no comorbidities, n	9,332	9,371	18,703
Participants with ≥8 weeks follow-up, %	70.0	69.9	70.0
Median follow-up post-vaccination, days	64.0	64.0	64.0
18−59 years, with comorbidities, n	5,232	5,176	10,408
Participants with ≥8 weeks follow-up, %	49.9	50.8	50.4
Median follow-up post-vaccination, days	56.0	57.0	57.0
≥60 years, overall, n	7,331	7,341	14,672
Participants with ≥8 weeks follow-up, %	38.2	37.8	38.0
Median follow-up post-vaccination, days	52.0	52.0	52.0
≥60 years, no comorbidities, n	3,627	3,595	7,222
Participants with ≥8 weeks follow-up, %	47.6	49.0	48.3
Median follow-up post-vaccination, days	54.0	55.0	54.0
≥60 years, with comorbidities, n	3,704	3,746	7,450
Participants with ≥8 weeks follow-up, %	29.0	27.1	28.0
Median follow-up post-vaccination, days	50.0	50.0	50.0

Table S6. Unsolicited Adverse Events of Grade ≥3 Considered Related to Ad26.COV2.S or Placebo

	Number (%) participants	
	Ad26.COV2.S	**Placebo**
Full Analysis Set	**N=21,895**	**N=21,888**
Any event	20 (0.1)	11 (0.1)
Nervous system disorders	7 (<0.1)	3 (<0.1)
Headache	4 (<0.1)	2 (<0.1)
Guillain-Barré Syndrome	1 (<0.1)	0
Radiculitis brachial	1 (<0.1)	0
Syncope	1 (<0.1)	0
Dizziness	0	1 (<0.1)
General disorders and administration site conditions	6 (<0.1)	2 (<0.1)
Fatigue	2 (<0.1)	2 (<0.1)
Chills	1 (<0.1)	0
Malaise	1 (<0.1)	1 (<0.1)
Pyrexia	1 (<0.1)	0
Vaccination site hypersensitivity	1 (<0.1)	0
Asthenia	0	1 (<0.1)
Gastrointestinal disorders	4 (<0.1)	2 (<0.1)
Nausea	2 (<0.1)	0
Diarrhea	1 (<0.1)	1 (<0.1)
Dyspepsia	1 (<0.1)	0
Vomiting	1 (<0.1)	0
Abdominal pain	0	1 (<0.1)
Musculoskeletal and connective tissue disorders	3 (<0.1)	2 (<0.1)
Myalgia	1 (<0.1)	1 (<0.1)
Pain in extremity	1 (<0.1)	0
Tendon disorder	1 (<0.1)	0
Arthralgia	0	1 (<0.1)
Cardiac disorders	2 (<0.1)	2 (<0.1)
Pericarditis	1 (<0.1)	0
Tachycardia	1 (<0.1)	0
Atrial fibrillation	0	1 (<0.1)
Atrial flutter	0	1 (<0.1)
Injury, poisoning and procedural complications	1 (<0.1)	0
Post-vaccination syndrome	1 (<0.1)	0
Respiratory, thoracic and mediastinal disorders	1 (<0.1)	1 (<0.1)
Nasal congestion	1 (<0.1)	1 (<0.1)
Sneezing	0	1 (<0.1)
Wheezing	0	1 (<0.1)
Ear and labyrinth disorders	0	1 (<0.1)
Vertigo	0	1 (<0.1)
Infections and infestations	0	2 (<0.1)
Epstein-Barr virus	0	1 (<0.1)
Fungal skin infection	0	1 (<0.1)
Vascular disorders	0	2 (<0.1)

Deep vein thrombosis	0	1 (<0.1)
Systolic hypertension	0	1 (<0.1)
Safety set	**N=3,356**	**N=3,380**
Any event	5 (0.1)	1 (<0.1)
Nervous system disorders	1 (<0.1)	1 (<0.1)
Headache	1 (<0.1)	0
Dizziness	0	1 (<0.1)
General disorders and administration site conditions	3 (0.1)	0
Fatigue	1 (<0.1)	0
Chills	1 (<0.1)	0
Malaise	1 (<0.1)	0
Gastrointestinal disorders	1 (<0.1)	0
Diarrhea	1 (<0.1)	0
Musculoskeletal and connective tissue disorders	1 (<0.1)	1 (<0.1)
Pain in extremity	1 (<0.1)	0
Arthralgia	0	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	0	1 (<0.1)
Nasal congestion	0	1 (<0.1)
Sneezing	0	1 (<0.1)
Wheezing	0	1 (<0.1)

The safety subset comprised approximately 6,000 participants who recorded solicited local and systemic AEs in an electronic diary for 7 days post-vaccination and unsolicited AEs for 28 days post-vaccination.

Table S7. Summary of Unsolicited AEs, SAEs and Other Events of Interest

	Ad26.COV2.S	Placebo
Unsolicited AEs during 28-day post-vaccination period, number (%) of participants	N=3,356[1]	N=3,380[1]
Any unsolicited AE	440 (13.1%)	407 (12.0%)
Unsolicited AE grade ≥3	19 (0.6%)	18 (0.5%)
Unsolicited AE reported by ≥10% of participants	0	0
SAEs, number (%) of participants	N=21,895[2]	N=21,888[2]
Any SAE not related to COVID-19	83 (0.4%)	96 (0.4%)
SAE considered related to vaccination	7	2
Guillain-Barré syndrome	1	0
Pericarditis	1	0
Brachial radiculitis	1	0
Hypersensitivity	1	0
Bell's palsy	2	0
Deep vein thrombosis	0	1
Epstein-Barr virus infection	0	1[3]
Atrial flutter	0	1[3]
Post-vaccination syndrome[4]	1	0
AEs of interest,[5] number of cases	N=21,895[2]	N=21,888[2]
Urticaria (non-serious)	8	5
Hypersensitivity[6]	9	6
Peripheral neuropathy	2	2
Guillain-Barré syndrome	1	1
Bell's palsy	3	2
AEs occurring more frequently in the Ad26.COV2.S group versus placebo group, number of cases	N=21,895[2]	N=21,888[2]
Deep vein thrombosis	6	2
Pulmonary embolism	4	1
Transverse sinus thrombosis	1	0
Seizure	4	1
Tinnitus	6	0
Deaths[7]	N=21,895[2]	N=21,888[2]
Deaths	3	16

[1]Safety subset (N=3,356 Ad26.COV2.S; N=3,380 placebo)

[2]Full analysis set (N=21,895 Ad26.COV2.S; N=21,888 placebo)

[3]Epstein-Barr virus infection and atrial flutter occurred in the same participant

[4]Severe generalized weakness, fever, and headache

[5]Including but not limited to allergic, neurologic, inflammatory, vascular, and autoimmune disorders

[6]Includes one related SAE of Type IV (delayed) hypersensitivity

[7]Deaths in the Ad26.COV2.S group were: unspecified reason (not COVID-19), lung abscess (not COVID-19), and pneumonia (not COVID-19). Deaths in the placebo group were: suicide (not COVID-19), acute myocardial infarction (not COVID-19), unspecified reason (two participants, not COVID-19), accidental overdose (not COVID-19), sudden death (not COVID-19), pneumonia (not COVID-19), malaise (not COVID-19), cardiac failure (confirmed COVID-19), COVID-19 (3 participants, confirmed COVID-19), COVID-19 pneumonia (2 participants, one RT-PCR-positive at baseline, confirmed COVID-19), pneumonia (probable COVID-19), suspected COVID-19 (probable COVID-19)

AE: adverse event; SAE: serious adverse event

Table S8. Description of Venous Thromboembolic Events

Study intervention	Age, gender	Preferred term	Serious	Time to onset (days)	Outcome	Relationship[1]	Relevant family or medical history	Case notes
Ad26.COV2.S	63 Male	Deep vein thrombosis	Yes	22	Recovered	Not related	Depression, obesity and a 'genetic mutation that made him susceptible to thromboembolism'	Discontinued rivaroxaban as 'he did not like taking it' 7 months prior to onset, following his retirement
Ad26.COV2.S	52 Male	Deep vein thrombosis	No	27	Recovering	Related	Obesity	
Ad26.COV2.S	42 Male	Deep vein thrombosis	No	19	Not recovered	Not related		Developed COVID-19 2 weeks prior to onset
Ad26.COV2.S	90 Male	Deep vein thrombosis	No	13	Recovering	Not related	Chronic kidney disease, hypertension, hypothyroidism, major depression	Event was secondary to trauma
Ad26.COV2.S	63 Male	Deep vein thrombosis	No	23	Recovered	Not related	Hypertension, diabetes	
Ad26.COV2.S	72 Male	Deep vein thrombosis	Yes	36	Not recovered	Not related	Hypertension, obesity	Positive COVID-19 case. While hospitalized, participant developed kidney failure and pulmonary embolism
Placebo	44 Male	Deep vein thrombosis	Yes	6	Not recovered	Related	3 paternal uncles with deep vein thrombosis, 4.5-hour air travel 4 days after vaccination (1 day to onset of symptoms)	
Placebo	57 Male	Deep vein thrombosis	No	3	Not recovered	Not related	Obesity, deep vein thrombosis, hypothyroidism, oropharyngeal cancer	
Ad26.COV2.S	30 Female	Pulmonary embolism	Yes	3	Recovered	Not related	Drug and alcohol abuse, contraceptive use (medroxyprogesterone)	

Ad26.COV2.S	66 Male	Pulmonary embolism	Yes	57	Not recovered	Not related	Pulmonary embolism, hypertension, spinal stenosis, high cholesterol	
Ad26.COV2.S	54 Male	Pulmonary embolism	Yes	45	Recovered	Not related	Obesity, hypertension, hereditary hemochromatosis	
Ad26.COV2.S	68 Male	Pulmonary embolism	No	20	Not recovered	Not related	COPD, hypertension, dyslipidemia, gout, hypothyroidism, insulin resistance, tonsillitis, urinary tract infection	
Placebo	53 Male	Pulmonary embolism	Yes	29	Recovering	Not related	Obesity, obstructive sleep apnea, hyperlipidemia, hypertension	Positive COVID-19 test
Ad26.CoV2.S	25 Male	Transverse sinus thrombosis, cerebral hemorrhage	Yes	21	Recovered	Not related	None of relevance for the event	Event most likely resulted from multiple pre-disposing factors including pre-existing cerebral sigmoid sinus stenosis that pre-disposed the participant to cerebral venous thrombosis, and an infection with an unknown organism that started 8 days following vaccination, triggering inflammation and a hypercoagulable state. Thrombocytopenia also observed. Subsequent testing identified anti-PF4 antibodies at the time of the event.

[1]Relationship to vaccine or placebo as determined by the Principal Investigator

COPD: chronic obstructive pulmonary disease

Table S9. Vaccine Efficacy Against COVID-19 With Onset At Least 1 Day After Vaccination (Full Analysis Set, Seronegative At Baseline)

	Ad26.COV2.S N=19,744[2]		Placebo N=19,822[2]		VE (95% CI)[1]
	No. cases	PY	No. cases	PY	
Moderate to severe–critical COVID-19	193	3,183.0	432	3,172.8	55.5% (47.1, 62.6)
18−59 years	151	2,150.6	316	2,146.8	52.3% (41.9, 61.0)
≥60 years	42	1,032.5	116	1,026.0	64.0% (48.4, 75.3)
Symptomatic COVID-19, any severity	195	3,182.8	435	3,172.6	55.3% (47.0, 62.5)
Mild	2	3,182.8	3	3,172.6	Not calculated[3]
Moderate	172	3,183.0	354	3,172.8	51.6% (41.7, 59.9)
Severe–critical	21	3,201.5	78	3,207.9	73.0% (55.9, 84.2)
Severity-adjusted symptomatic COVID-19[4]	195	3,182.8	435	3,172.6	57.9% (49.7, 64.6)
18−59 years	152	2,150.5	316	2,146.8	54.9% (44.8, 63.0)
≥60 years	43	1,032.3	119	1,025.8	65.3% (49.8, 75.8)
Moderate to severe–critical COVID-19 including non centrally-confirmed cases	263	3,178.8	617	3,163.2	57.6% (50.9, 63.4)
COVID-19 using US FDA harmonized definition	192	3,182.9	429	3,173.0	55.4% (47.0, 62.6)

All cases were centrally-confirmed unless stated otherwise.

Follow-up time for each participant was defined as time since vaccination until onset of a COVID-19 episode or the last available study measurement (22 January 2021).

[1]Unadjusted 95% CIs shown

[2]At-risk population: excludes participants who were seropositive at baseline

[3]VE not calculated if fewer than 6 cases were observed for an endpoint

[4]Weighted version of mild, moderate and severe–critical VE estimates (Mehrotra et al, 2021)[4]

CI: confidence interval; FDA: Food and Drug Administration; PY: person-years; VE: vaccine efficacy

Table S10. Vaccine Efficacy Against COVID-19 Requiring Medical Intervention (Per-Protocol Set, Seronegative At Baseline)

	Ad26.COV2.S		Placebo		VE (95% CI)
	N	Number of cases	N	Number of cases	
Centrally-confirmed					
≥14 days	19,514[1]	2	19,544[1]	8	75.0% (-25.3, 97.4)
≥28 days	19,306[2]	0	19,178[2]	5	Not calculated[3]
RT-PCR-positive from all sources					
≥14 days	19,514[1]	2	19,544[1]	14	85.7% (37.8, 98.4)
≥28 days	19,306[2]	0	19,178[2]	7	100.0% (31.1, 100.0)

[1]At-risk population: excludes participants who were RT-PCR positive between Day 1 and Day 14

[2]At-risk population: excludes participants who were RT-PCR positive between Day 1 and Day 28

[3]VE not calculated if fewer than 6 cases were observed for an endpoint

The first occurrence of COVID-19 requiring medical intervention was defined as requiring hospitalization, ICU admission, mechanical ventilation, or ECMO, linked to objective measures such as decreased oxygenation, X-ray or CT findings or linked to any molecularly confirmed, COVID-19 during a COVID-19 episode with onset ≥14 days and ≥28 days post-vaccination. This information was collected based on the MRU questionnaire as pre-specified in the statistical analysis plan and does not include all hospitalizations identified by SAE forms or MA-COV forms (pre-specified analysis).

CI: confidence interval; CT: computed tomography; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; MA-COV: medically-attended COVID-19; MRU: medical resource use; SAE: serious adverse event; VE: vaccine efficacy

Table S11. Vaccine Efficacy Against Moderate to Severe–Critical COVID-19 With Onset At Least 14 and 28 Days After Vaccination in the United States By Race and Ethnicity (Per-Protocol Set, Seronegative At Baseline, RT-PCR-positive Cases from All Sources)

	At least 14 days post-vaccination							At least 28 days post-vaccination						
	Ad26.COV2.S N=9,119[2]			Placebo N=9,086[2]			VE (95% CI)[1]	Ad26.COV2.S N=8,958[3]			Placebo N=8,835[3]			VE (95% CI)[1]
	N	No. cases	PY	N	No. cases	PY		N	No. cases	PY	N	No. cases	PY	
Race														
American Indian or Alaskan Native	86	1	12.0	89	2	12.4	Not calculated[4]	84	1	11.7	87	1	12.3	Not calculated[4]
Asian	635	4	87.2	565	9	77.7	60.4% (-42.0, 91.1)	611	1	85.7	544	6	76.3	85.2% (-22.3, 99.7)
Black or African American	1,113	4	149.3	1,124	18	149.4	77.8% (32.5, 94.5)	1,098	2	148.3	1,095	7	147.6	71.6% (-49.4, 97.1)
Native Hawaiian or other Pacific Islander	43	0	6.3	38	0	5.7	Not calculated[4]	43	0	6.3	37	0	5.6	Not calculated[4]
White	6,774	40	1,095.2	6,751	157	1,076.2	75.0% (64.4, 82.8)	6,664	27	1,087.9	6,572	93	1,064.9	71.6% (56.0, 82.2)
Multiracial	171	1	23.7	169	2	22.5	Not calculated[4]	166	0	23.3	163	1	22.2	Not calculated[4]
Unknown	123	0	16.8	129	3	18.2	Not calculated[4]	122	0	16.7	124	2	17.9	Not calculated[4]
Not reported	173	1	23.4	219	5	29.1	75.2% (-121.5, 99.5)	169	1	23.2	211	2	28.6	Not calculated[4]
Missing	1	0	0.1	2	0	0.3	Not calculated[4]	1	0	0.1	2	0	0.3	Not calculated[4]
Ethnicity														
Hispanic or Latino	1,252	6	170.2	1,322	27	180.6	76.4% (41.7, 92.0)	1,228	3	168.5	1,273	15	177.7	78.9% (25.4, 96.1)

Not Hispanic or Latino	7,601	44	1,204.5	7,474	161	1,169.4	73.5% (62.8, 81.4)	7,466	28	1,195.7	7,279	92	1157.0	70.5% (54.6, 81.4)
Unknown	78	0	11.4	77	3	11.0	Not calculated[4]	77	0	11.4	75	1	10.9	Not calculated[4]
Not reported	187	1	27.7	212	5	30.2	78.2% (-94.8, 99.5)	186	1	27.6	207	4	29.8	Not calculated[4]
Missing	1	0	0.2	1	0	0.2	Not calculated[4]	1	0	0.2	1	0	0.2	Not calculated[4]

[1]Unadjusted 95% CIs

[2]At-risk population: excludes participants who were RT-PCR positive between Day 1 and Day 14

[3]At-risk population: excludes participants who were RT-PCR positive between Day 1 and Day 28

[4]VE not calculated if fewer than 6 cases were observed for an endpoint

CI: confidence interval; PY: person-years; RT-PCR: reverse transcriptase polymerase chain reaction; VE: vaccine efficacy

References

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